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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 08/23/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

S.M.

Office Action Summary	Application No.	Applicant(s)	
	10/071,136	EDWARDS, DAVID N.	
	Examiner	Art Unit	
	Jehanne Souaya Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *NA*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner reviewing your application at the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to examiner Jehanne Sitton.

2. Currently claims 1-13 are pending in the instant application. This case has been withdrawn from issue because prior art was found with regard to the claims. The following rejections constitute the complete set being presently applied to the instant application. This action is NON-FINAL.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1 and 9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant case, dependent claim 9, and therefore, independent claim 1, includes a recitation to 'adenoviral hemagluttinin'. The specification provides no more description of 'adenoviral hemagluttinin' than to recite that it is part of the invention contemplated for sequences which comprise the common peptide. A thorough review of

the specification provides no description of an immunological epitope from 'adenoviral hemagluttinin', and a thorough review of the prior art provides no teaching of the structure of such immunological epitopes. However, Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.) Additionally, the courts have held that adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written

description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Therefore, absent a description of the structure or sequence of an immunological epitope from adenoviral hemagluttinin, (which the examiner also could not find in the prior art), the specification does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

6. Claims 1-4, 10, 11, and 13 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Thukral, S.K. (US Patent 6,103,472, 102(a): August 15, 2000, 102(e) date: 2/20/1998).

Thukral teaches a method of constructing a cDNA library and inserting the library into a signal trap vector to generate a signal trap library (hybrid gene library of instant claim 1, see col. 2, lines 40-50). The signal trap library (hybrid gene library) taught by Thukral is constructed with vectors such that DNA sequences which control expression

of selection or marker genes, cDNA inserts, and reporter genes are operably linked to said cDNA and genes and that the signal sequences are inserted in frame to the reporter polypeptide coding sequences (see col. 7, lines 5-15). Thukral teaches that the vector is pYYa-41L which is an E. coli –yeast shuttle vector that contains a Bla1 gene for ampicillin resistance and TRP1 gene for propagation in yeast ('selectable marker sequence' with regard to instant claim 1, and instant claim 11, see col. 7, lines 15-19). Thukral teaches that the vector contains ColE1-ORI replication origin for maintenance and propagation in E coli (instant claim 2), and a 2u origin for replication and propagation in yeast (instant claims 3 and 10, see col. 7, lines 15-19). With regard to instant claim 1, Thukral also teaches that the vector contains in order 5' to 3' an ADH promoter (regulatable DNA sequence), a polylinker containing unique XhI and Not I sites to facilitate directional cloning of random primed cDNAs (multiple cloning site that does not encode a translational termination sequence and placed immediately 3' to the regulatable DNA sequence, see also col. 10, lines 34-37), a leaderless a-amylase gene encoding amino acids 29-624 of a-amylase (a DNA sequence encoding at least one common peptide and not containing a translation initiation codon which is place 3' to the multiple cloning site) (see col. 7, lines 20-26), or amino acids 82-624 (see col. 10, lines 58-67). See also example 3 for construction of hybrid gene cDNA library. Although Thukral does not explicitly state that the multiple cloning site does not contain a translational termination sequence, such is an inherent teaching of Thukral because the hybrid protein that is constructed, as taught by Thukral, contains the protein encoded by the random primed cDNA on the N-terminal side fused to the leaderless a-amylase protein (common peptide) on the C-terminal side. With regard to instant claims 4 and 13,

Thukral teaches that after the a-amylase sequence, the vector contains an ADH terminator sequence (see col. 7, lines 23 and 24).

7. Claims 1-3 are rejected under 35 U.S.C. 102(b) as being anticipated by Fields et al; US Patent 5,468,614.

With respect to claim 1, Fields teaches a kit for making, as well as vector libraries which include a 'second vector' which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vector in the library contains a promoter, a transcription termination signal and a chimeric gene that includes a DNA sequence that encodes a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a library of plasmids that contain genomic, cDNA , or synthetically generated DNA sequences fused to the DNA sequence encoding the transcriptional activation domain. Fields specifically exemplifies vectors which contains the SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein. Fields inherently teaches a vector which contains a single cDNA molecule which is 5' of the common peptide encoding sequence (GAL4), wherein the common peptide does not contain a translation initiation codon. Additionally, the vectors of the library of Fields could not have a translational

termination sequence at the multiple cloning site because the common peptide GAL4, would not be fused to the C terminal end of SNF4 gene after translation, should one exist. Additionally, the recitation of "wherein each vector of the library additionally comprises a single cDNA molecule inserted at the multiple cloning site wherein each of said cDNA molecules is obtained from a cDNA population generated using random primers" imparts no structural limitation on the cDNA library and therefore has been given no patentable weight. Additionally, the term library has been broadly interpreted to encompass as few as 2 vectors, which could contain the same sequences, as such could be the result of cDNA population generated using random primers".

With regards to claims 2 and 3, Fields specifically teaches that the 'second vector' further includes a means for replicating itself in the host cell, which Fields specifically teaches encompasses yeast cells (see col. 4, lines 21-22), and in bacteria (see col. 5-6, bridging para).

Fields also teaches that the 'second vector' contains a marker gene which permits selection of cells containing the marker gene from cells which do not contain it (col 6, lines 1-5).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 4 and 10-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of Thukral.

Fields teaches a kit for making, as well as vector libraries which include a 'second vector' which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vector in the library contains a promoter, a transcription termination signal and a chimeric gene that includes a DNA sequence that encodes a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a library of plasmids that contain genomic, cDNA , or synthetically generated DNA sequences fused to the DNA sequence encoding the transcriptional activation domain. Fields specifically exemplifies vectors which contains the SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein. Fields inherently teaches a vector which contains a single cDNA molecule which is 5' of the common peptide encoding sequence (GAL4), wherein the common peptide does not contain a translation initiation codon. Additionally, the vectors of the library of Fields could not have a translational termination sequence at the multiple cloning site because the common peptide GAL4, would not be fused to the C terminal end of SNF4 gene after translation, should one exist. Additionally, the recitation of "wherein each vector of the library additionally comprises a single cDNA molecule inserted at the multiple cloning

site wherein each of said cDNA molecules is obtained from a cDNA population generated using random primers" imparts no structural limitation on the cDNA library and therefore has been given no patentable weight. Additionally, the term library has been broadly interpreted to encompass as few as 2 vectors, which could contain the same sequences, as such could be the result of cDNA population generated using random primers". Fields specifically teaches that the 'second vector' further includes a means for replicating itself in the host cell, which Fields specifically teaches encompasses yeast cells (see col. 4, lines 21-22), and in bacteria (see col. 5-6, bridging para). Fields also teaches that the 'second vector' contains a marker gene which permits selection of cells containing the marker gene from cells which do not contain it. Although Fields teaches that the vectors include a transcriptional termination sequence, Fields does not specifically teach one that is placed immediately 3' to the DNA sequence encoding at least one common peptide (claim 4), which is the ADH1 termination sequence (claim 13). Fields also does not specifically teach the yeast origin of replication that is derived from the natural 2 micron yeast plasmid (claim 10). Additionally, Fields does not teach selectable marker sequences: bacterial ampicillin gene and TRP 1 nutritional auxotrophy gene (claim 11) or bacterial kanamycin resistance gene and yeast URA3 nutritional auxotrophy gene.

However, Thukral teaches and exemplifies a method of constructing a hybrid gene cDNA library. The vectors in the library exemplified by Thukral contain, 5' to 3', a promoter (yeast ADH 1 promoter), a polylinker containing restriction sites for directional cloning of random primed cDNAs, a common peptide, and a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide (col. 10, lines

34-37; col. 7, lines 20-26; col. 10, lines 58-67). See also example 3 for construction of hybrid gene cDNA library. Although Thukral does not explicitly state that the multiple cloning site does not contain a translational termination sequence, such is a property of the teaching of Thukral because the hybrid protein that is constructed, as taught by Thukral, contains the protein encoded by the random primed cDNA on the N-terminal side fused to the leaderless a-amylase protein (common peptide) on the C-terminal side.

With regard to instant claims 4 and 13, Thukral teaches that after the a-amylase sequence, the vector contains an ADH terminator sequence (see col. 7, lines 23 and 24). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vector for hybrid gene libraries as taught by Fields and to include a transcriptional terminator sequence immediately 3' to the common peptide to achieve the expected advantage of producing a hybrid protein with a test protein on the amino terminal end of the protein and the common peptide on the C terminal end, as taught by both Fields and Thukral. For a hybrid protein to be produced as taught by both Fields and Thukral, a transcriptional terminator sequence would need to be present to ensure that the common peptide is on the C terminal end of the hybrid protein. The ordinary artisan would have been motivated to include a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide to achieve a hybrid protein as taught by both Fields and Thukral. Additionally, Thukral specifically teaches to construct a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide to construct a hybrid protein as taught by Thukral. The ordinary artisan would have been further motivated to include the transcriptional terminator sequence of ADH1 because Thukral teaches that such

successfully functions in constructing hybrid gene libraries that produce hybrid proteins as taught by both Fields and Thukral.

With regard to instant claims 11 and 12, Thukral teaches that the vector should contain marker genes such as a gene for ampicillin resistance, or a gene for bacterial kanamycin resistance for growth in bacterial, and TRP1 gene or URA gene for propagation in yeast (see col. 7, lines 15-19; col. 4 line 67; col. 5, lines 4-5). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vector for hybrid gene libraries as taught by Fields and to include specific selection markers as taught by Thukral to achieve the expected advantage of constructing a vector which allows for selection of cells containing the marker gene from cells which do not contain it, as taught by Fields. The ordinary artisan would have been motivated to include the marker genes as taught by Thukral because Fields teaches that vectors should contain a marker and Thukral teaches that marker genes include those for ampicillin or kanamycin resistance in bacteria and URA or TRP1 for propagation in yeast. As Fields teaches that the vectors should be capable of propagation in different host cells including yeast and bacteria, the ordinary artisan would have been further motivated to include selectable markers for propagation in yeast and bacteria in the same vector, as taught and exemplified by Thukral, for the purpose of constructing a more versatile vector that would allow for propagation in different types of host cells, such as yeast and bacteria. The ordinary artisan would have had a reasonable expectation of success that a vector could be constructed in this way, because Thukral teaches the successful construction of vectors that contain selectable markers for both bacteria and yeast, in the same vector.

With regard to instant claim 10, Thukral teaches that the vector contains ColE1-ORI replication origin for maintenance and propagation in E coli (instant claim 2), and a 2u origin for replication and propagation in yeast (see col. 7, lines 15-19). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vector for hybrid gene libraries as taught by Fields and to include origin of replication for both E. coli and yeast, as specifically taught by Thukral to achieve the expected advantage of constructing a vector which allows for propagation of vectors in either a bacteria or yeast host cell as taught by Fields. The ordinary artisan would have been motivated to include the origin of replication for yeast as taught by Thukral because Fields teaches that vectors should be replicatable in either bacteria or yeast and Thukral teaches origin of replication for yeast include that derived from the natural 2-micron yeast plasmid. As Fields teaches that the vectors should be capable of propagation in different host cells including yeast and bacteria, the ordinary artisan would have been further motivated to include origins of replication for yeast and bacteria in the same vector, as taught and exemplified by Thukral, for the purpose of constructing a more versatile vector that would allow for propagation in different types of host cells, such as yeast and bacteria. The ordinary artisan would have had a reasonable expectation of success that a vector could be constructed in this way, because Thukral teaches the successful construction of vectors that contain origins of replication for both yeast and bacteria.

10. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over, in the alternative, Fields or Thukral, each in view of Carson et al (US Patent, 5,679,647).

Fields teaches a kit for making, as well as vector libraries which include a 'second vector' which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vector in the library contains a promoter, a transcription termination signal and a chimeric gene that includes a DNA sequence that encodes a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a library of plasmids that contain genomic, cDNA, or synthetically generated DNA sequences fused to the DNA sequence encoding the transcriptional activation domain. Fields specifically exemplifies vectors which contain the SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein. Fields teaches a vector which contains a single cDNA molecule which is 5' of the common peptide encoding sequence (GAL4 activation domain), wherein the common peptide does not contain a translation initiation codon. Additionally, the vectors of the library of Fields could not have a translational termination sequence at the multiple cloning site because the common peptide GAL4, would not be fused to the C terminal end of SNF4 gene after translation, should one exist. Additionally, the recitation of "wherein each vector of the library additionally comprises a single cDNA molecule inserted at the multiple cloning site wherein each of said cDNA molecules is obtained from a cDNA population generated using random primers" imparts no structural limitation on the

cDNA library and therefore has been given no patentable weight. Additionally, the term library has been broadly interpreted to encompass as few as 2 vectors, which could contain the same sequences, as such could be the result of cDNA population generated using random primers".

Thukral teaches and exemplifies a method of constructing a hybrid gene cDNA library. The vectors in the library exemplified by Thukral contain, 5' to 3', a promoter (yeast ADH 1 promoter), a polylinker containing restriction sites for directional cloning of random primed cDNAs, a common peptide, and a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide (col. 10, lines 34-37; col. 7, lines 20-26; col. 10, lines 58-67). See also example 3 for construction of hybrid gene cDNA library. Although Thukral does not explicitly state that the multiple cloning site does not contain a translational termination sequence, such is a property of the teaching of Thukral because the hybrid protein that is constructed, as taught by Thukral, contains the protein encoded by the random primed cDNA on the N-terminal side fused to the leaderless a-amylase protein (common peptide) on the C-terminal side.

Neither Fields nor Thukral teach a hybrid gene cDNA library wherein the regulatable DNA sequence is the rat Glucorticoid Response element. However, Carson teaches an expression system that exploits glucocorticoid response elements responsive to a wide variety of steroid hormones and teaches that pGREtk plasmid, which contains one or more rat tyrosine amino transferase glucocorticoid response elements upstream of the thymidine kinase promoter from pBLCAT8+, makes the pGREtk promoter particularly effective in stimulating controlled overexpression of cloned genes in eukaryotic cells (see col. 14, lines 40-55). Therefore, it would have been prima facie obvious to one of

ordinary skill in the art at the time the invention was made to improve the regulatable DNA sequence in the vector used for making hybrid gene cDNA libraries of either Fields or Thukral, by including rat glucocorticoid response element for the purpose of making the regulatable DNA sequence in the vectors of either Fields or Thukral more effective in stimulating the controlled expression of cloned genes in eukaryotic cells. The ordinary artisan would have been motivated to include rat glucocorticoid response element in the vector of either Fields or Thukral because Carson teaches that using such response element is effective in stimulating the controlled expression of cloned genes in eukaryotic cells.

11. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over, in the alternative, Fields or Thukral, each in view of Le Douarin et al (Nucleic Acids Research, vol., 23, pages 876-878, 1995).

Fields teaches a kit for making, as well as vector libraries which include a 'second vector' which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vector in the library contains a promoter, a transcription termination signal and a chimeric gene that includes a DNA sequence that encodes a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a library of plasmids that contain genomic, cDNA, or synthetically generated DNA sequences fused to the DNA sequence encoding

the transcriptional activation domain. Fields specifically exemplifies vectors which contain the SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein. Fields teaches a vector which contains a single cDNA molecule which is 5' of the common peptide encoding sequence (GAL4 activation domain), wherein the common peptide does not contain a translation initiation codon. Additionally, the vectors of the library of Fields could not have a translational termination sequence at the multiple cloning site because the common peptide GAL4, would not be fused to the C terminal end of SNF4 gene after translation, should one exist. Additionally, the recitation of "wherein each vector of the library additionally comprises a single cDNA molecule inserted at the multiple cloning site wherein each of said cDNA molecules is obtained from a cDNA population generated using random primers" imparts no structural limitation on the cDNA library and therefore has been given no patentable weight. Additionally, the term library has been broadly interpreted to encompass as few as 2 vectors, which could contain the same sequences, as such could be the result of cDNA population generated using random primers".

Thukral teaches and exemplifies a method of constructing a hybrid gene cDNA library. The vectors in the library exemplified by Thukral contain, 5' to 3', a promoter (yeast ADH 1 promoter), a polylinker containing restriction sites for directional cloning of random primed cDNAs, a common peptide, and a transcriptional terminator sequence immediately 3' to the sequence encoding the common peptide (col. 10, lines 34-37; col. 7, lines 20-26; col. 10, lines 58-67). See also example 3 for construction of hybrid gene

cDNA library. Although Thukral does not explicitly state that the multiple cloning site does not contain a translational termination sequence, such is a property of the teaching of Thukral because the hybrid protein that is constructed, as taught by Thukral, contains the protein encoded by the random primed cDNA on the N-terminal side fused to the leaderless a-amylase protein (common peptide) on the C-terminal side.

Neither Fields nor Thukral teach a hybrid gene cDNA library wherein the regulatable DNA sequence is an estrogen response element. However, Le Douarin teaches a two hybrid assay which involves hybrid gene cDNA libraries wherein the vectors contain an integrated URA3 reporter gene driven by one or three estrogen receptor response elements (see page 876, col. 1, 2nd para). Le Douarin teaches that such system is particularly useful for large screening of acidic activation domain tagged cDNA libraries. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to improve the regulatable DNA sequence in the vector used for making hybrid gene cDNA libraries of either Fields or Thukral, by including an estrogen response element because Le Douarin teaches that such system is particularly useful for large screening of acidic activation domain tagged cDNA libraries. The ordinary artisan would have been motivated to improve the regulatable DNA sequence in the vector used for making hybrid gene cDNA libraries of either Fields or Thukral, by including an estrogen response element because Le Douarin teaches that such system is particularly useful for large screening of acidic activation domain tagged cDNA libraries.

12. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of Wagner et al (US patent 6,329,209).

Fields teaches a kit for making, as well as vector libraries which include a 'second vector' which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches that the vector in the library contains a promoter, a transcription termination signal and a chimeric gene that includes a DNA sequence that encodes a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a library of plasmids that contain genomic, cDNA, or synthetically generated DNA sequences fused to the DNA sequence encoding the transcriptional activation domain. Fields specifically exemplifies vectors which contain the SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein. Fields teaches a vector which contains a single cDNA molecule which is 5' of the common peptide encoding sequence (GAL4 activation domain), wherein the common peptide does not contain a translation initiation codon. Additionally, the vectors of the library of Fields could not have a translational termination sequence at the multiple cloning site because the common peptide GAL4, would not be fused to the C terminal end of SNF4 gene after translation, should one exist. Additionally, the recitation of "wherein each vector of the library additionally comprises a single cDNA molecule inserted at the

multiple cloning site wherein each of said cDNA molecules is obtained from a cDNA population generated using random primers" imparts no structural limitation on the cDNA library and therefore has been given no patentable weight. Additionally, the term library has been broadly interpreted to encompass as few as 2 vectors, which could contain the same sequences, as such could be the result of cDNA population generated using random primers".

Fields does not teach a common peptide encoded by a molecule comprising sequence encoding all or part of the GAL4 yeast transcriptional activator and 6 successive histidine residues. However, Wagner teaches that proteins expressed by cDNA libraries can be purified wherein the proteins to be expressed which are encoded by the cDNA library are genetically fused to a histidine tag. Therefore, it would have been prima facie obvious to one of ordinary skill in the art to modify the chimeric GAL4 activation domain protein of Fields to include a sequence within the vector of Fields that encoded both the GAL4 activation domain as well as 6 successive histidine tags because Wagner teaches that a histidine tag when genetically fused to an expressed peptide, allows the peptide expressed from a cDNA library to be purified. The ordinary artisan would have been motivated to modify the chimeric protein of Fields to include a histidine tag for the purpose of making the chimeric protein easier to purify.

13. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Fields in view of He et al (US Patent, 5,679,566).

Fields teaches a kit for making, as well as vector libraries which include a 'second vector' which contains a 'second chimeric gene' (see col. 5, lines 40-45). Fields teaches

that the vector in the library contains a promoter, a transcription termination signal and a chimeric gene that includes a DNA sequence that encodes a transcriptional activation domain and a unique restriction site(s) to insert a DNA sequence encoding a test protein or protein fragment into the vector such that a second hybrid protein is formed (see col. 5, lines 45-50) which is composed of the test protein fused to the transcriptional activation domain. Fields teaches that the activation domain can be that of GAL4 and teaches that the second hybrid protein may be encoded on a library of plasmids that contain genomic, cDNA, or synthetically generated DNA sequences fused to the DNA sequence encoding the transcriptional activation domain. Fields specifically exemplifies vectors which contain the SNF4 promoter (regulatable DNA sequence) and SNF4 gene lacking the last amino acid of SNF4 (see col. 9, lines 12-15; and col. 11, lines 2-5) fused to the GAL4 activation domain (amino acids 768-881) to form an SNF4-GAL4 fusion protein. Fields teaches a vector which contains a single cDNA molecule which is 5' of the common peptide encoding sequence (GAL4 activation domain), wherein the common peptide does not contain a translation initiation codon. Additionally, the vectors of the library of Fields could not have a translational termination sequence at the multiple cloning site because the common peptide GAL4, would not be fused to the C terminal end of SNF4 gene after translation, should one exist. Additionally, the recitation of "wherein each vector of the library additionally comprises a single cDNA molecule inserted at the multiple cloning site wherein each of said cDNA molecules is obtained from a cDNA population generated using random primers" imparts no structural limitation on the cDNA library and therefore has been given no patentable weight. Additionally, the term library has been broadly interpreted to encompass as few as 2 vectors, which could

contain the same sequences, as such could be the result of cDNA population generated using random primers".

Fields does not teach a common peptide encoded by a molecule comprising sequence encoding all or part of the GAL4 yeast transcriptional activator and a nuclear localization sequence from SV40 virus. However, He teaches that GAL4-activation domain fusion proteins were targeted to the nucleus using the SV40 T antigen nuclear localization signal (NLS) (see col. 18, lines 10-45). He teaches that without the SV40 NLS, no B-galactosidase activity was detectable because nuclear localization had been eliminated. Therefore, it would have been prima facie obvious to one ordinary skill in the art at the time the invention was made to modify the chimeric GAL4 activation domain protein of Fields to include a sequence within the vector of Fields that encoded both the GAL4 activation domain as well as SV40 NLS because He teaches that without the SV40 NLS, no B-galactosidase activity was detectable because nuclear localization had been eliminated. The ordinary artisan would have been motivated to modify the chimeric protein of Fields to include the SV40 NLS because Fields uses B-galactosidase activity as a measure of interaction between the interaction of GAL4 DNA binding and GAL4 activation domain.

14. Claim 12 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thukral.

Thukral teaches a method of constructing a cDNA library and inserting the library into a signal trap vector to generate a signal trap library (hybrid gene library of instant claim 1, see col. 2, lines 40-50). The signal trap library (hybrid gene library) taught by Thukral is constructed with vectors such that DNA sequences which control expression

of section or marker genes, cDNA inserts, and reporter genes are operably linked to said cDNA and genes and that the signal sequences are inserted in frame to the reporter polypeptide coding sequences (see col. 7, lines 5-15). Thukral teaches that the vector is pYYa-41L which is an E. coli –yeast shuttle vector that contains a Bla1 gene for ampicillin resistance and TRP1 gene for propagation in yeast ('selectable marker sequence'). Thukral specifically teaches a vector which contains ColE1-ORI replication origin for maintenance and propagation in E coli (instant claim 2), and a 2u origin for replication and propagation in yeast (instant claims 3 and 10, see col. 7, lines 15-19). Thukral also teaches that the vector contains in order 5' to 3' an ADH promoter (regulatable DNA sequence), a polylinker containing unique XhI and Not I sites to facilitate directional cloning of random primed cDNAs (multiple cloning site that does not encode a translational termination sequence and placed immediately 3' to the regulatable DNA sequence, see also col. 10, lines 34-37), a leaderless a-amylase gene encoding amino acids 29-624 of a-amylase (a DNA sequence encoding at least one common peptide and not containing a translation initiation codon which is place 3' to the multiple cloning site) (see col. 7, lines 20-26), or amino acids 82-624 (see col. 10, lines 58-67). With regard to claim 12, although Thukral does not specifically teach a vector that contains selectable marker sequences such as the kanamycin for bacterial antibiotic resistance and the yeast URA3 nutritional auxotrophy gene, Thukral does teach that vectors can be constructed to contain selection genes such as URA (see col. 4 line 67) for growth in yeast and kanamycin for antibiotic resistance in bacteria (see col. 5, lines 4-5). Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to construct a vector for hybrid gene libraries that contained

as selection markers, the kanamycin gene and the URA gene because Thukral teaches that vectors for use in making such libraries can contain such selection genes. The ordinary artisan would have been motivated to construct a vector for hybrid gene libraries that contained as selection markers, the kanamycin gene and the URA gene because Thukral teaches to make vectors for use in making such libraries containing such selection genes.

Conclusion

15. No claims are allowable.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (571) 272-0782. The fax phone number for this Group is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
8/19/04